

**Remarks:**

The Office action makes multiple rejections under U.S.C. § 103(a). Claims 1-7, 11, 21-38 are rejected as being unpatentable over Desai et al. US 5916596. Claims 1-7, 11, 21-38 are also rejected as being unpatentable over Desai et al. US 5916596 in view of Popescu et al US 6090406. Claims 1-19 and 21-38 are rejected as being unpatentable over Violanto et al. US 4826689 in combination with Parikh US 5922355. Finally, Claims 1-19 and 21-38 are rejected as being unpatentable over Violanto et al. US 4826689 in combination with Parikh US 5922355, in view of Popescu US 6090406.

Applicants have amended Claims 1 and 25 to clarify that the in the applicants' method sonication takes place at a temperature below room temperature and causes the evaporation of essentially all of the water immiscible organic solvent to cause the pharmaceutically active agent to precipitate from the organic solvent into the aqueous solution. This amendment is supported by paragraph 35 and examples 1-8 of the applicants' specification.

Concerning the first § 103(a) rejection, the Office suggests that Desai's method of sonicating an emulsion anticipates the invention claimed by the applicants because Desai teaches a method of particle preparation by solvent evaporation technique from an oil-in-water emulsion prepared under conditions of high shear forces. The Office also suggests that sonication is well known in the art as an organic solvent removal method, and that "it would be obvious to one of ordinary skill in the art that the solvent could be removed without a further evaporation step because Desai teaches that the step is optional."

It is appreciated that the Office suggests that it is well known in the art to use sonication as an organic solvent removal method. However to support this view, the Office fails to point to art that demonstrates that sonication was known as method of solvent removal. Instead the

Office appears to be relying upon the cited Desai statement that “[o]ptionally, the organic and/or aqueous phases are thereafter removed from the mixture after having been subjected to high shear conditions.” (Desai col. 7, lines 52-54) Unlike the applicants that use sonication to remove solvent from an emulsion to cause a particles to precipitate, Desai’s statement neither teaches nor implies sonication as a known method of evaporation. Instead of implying shearing as a method of evaporation, the optional evaporation step of Desai cited by the Office appears to refer the fact that Desai’s particles can be either a solid or a liquid composition. (col 7, lines 58-60).

Therefore, Desai does not indicate that one skilled in the art would have known to use sonication as an organic solvent removal method.

Consequently, because the Office only pointed to Desai and Desai does not indicate that it would have been obvious to one of ordinary skill in the art to use sonication as an organic solvent removal method, reconsideration and withdrawal of the § 103(a) rejection of claims 1 and 25 are respectfully believed to be appropriate for these reasons. Because claims 2-7, 11, 21-24, and 30-34 are dependant upon claim 1 and claims 26-29 and 35-38 are dependant upon claim 25 reconsideration of the § 103(a) rejection of these claims are also respectfully believed to be appropriate.

In addition, Desai does not teach applicants’ claimed feature of sonication at a temperature below room temperature. Reconsideration and withdrawal of this § 103(a) rejection also are requested for this additional reason.

Concerning the second § 103(a) rejection the Office suggests that “Popescu discloses an example of using sonication to remove organic solvent such as ether from the reaction mixture. (col 23, lines 20-21).” However, Popescu does not teach sonication to remove organic solvents; instead, Popescu is evaporating the solvent by adding heat during sonication with the use of

47°C water bath. (col. 23 line 19). This temperature is 12 °C above the 35°C boiling point of diethyl ether, the solvent in the example of Popescu cited by the Office. (See material safety data sheet from Mallinckrodt Baker, Inc. <http://www.jtbaker.com/msds/englishhtml/E2340.htm>, print out copy attached). Therefore, unlike the applicants, Popescu's method of liposome preparation does not utilize sonication alone to evaporate organic solvents. Unlike the applicants, Popescu views sonication and evaporation as separate processes. As an alternative to heat, Popescu also states that his preparation can be dried "by a stream of nitrogen gas which drives off the organic solvent." (col 20 lines 9-14.) Popescu's view that sonication and evaporation are separate processes is confirmed in Lenk et al 4,522,803 which Popescu incorporates by reference at (col. 20, lines 11-14) to "further describe" their method of liposome preparation. ("This biphasic mixture is convert to SPLV [liposomes] by emulsifying the aqueous material within the solvent while evaporation the solvent. Evaporation can be accomplished during sonication by any evaporative technique, e.g. evaporation by passing a stream of inert gas over the mixture, by heating or by vacuum." (col 6, lines 28-33 of Lenk et al. 4,522,803).

Consequently, Popescu does not teach one of ordinary skill the art a method of sonicating a system to evaporate essentially all of the water immiscible organic solvent at a temperature below room temperature as applicants state in amended claims 1 and 25. Therefore, Popescu, even if properly combined with Desai, does not remove the deficiencies of Desai so as to make applicants' method obvious to one of ordinary skill in the art. Reconsideration and withdrawal of the § 103(a) rejection claims 1 and 25 from Desai et al. in view of Popescu et al. are respectfully believed to be appropriate for these reasons. Applicants' claims 2-7, 11, 21-24 and 30-34 are dependent on claim 1 and claims 26-29 and 35-38 are dependant upon claims 25, and

reconsideration and withdrawal of the § 103(a) rejection of these claims also are respectfully believed to be appropriate and requested.

Concerning the third § 103(a) rejection, the Office suggests that Violanto in combination with Parikh render applicants' claims 1-19 and 21-38 unpatentable. However, neither Violanto nor Parikh use sonication as a method of solvent removal to precipitate a pharmaceutically effective compound. In making this rejection the Office again suggests that "sonication as a method of solvent removal is well known in the art." As the Office does not cite art to support this conclusion in this third rejection, applicants presume that the Office is relying Desai and/or Popescu to demonstrate what was known in the art. As discussed in the previous two § 103(a) rejections, neither Desai nor Popescu indicate that sonication as a method of solvent removal was a method known in the art. Therefore it would not have been obvious to one of ordinary skill in the art to use sonication as an organic solvent removal method.

In addition, currently amended Claims 1 and 25 to clarify that the in the applicants' method sonication takes place at a temperature below room temperature causing the evaporation of essentially all of the water immiscible organic solvent to cause the pharmaceutically active agent to precipitate from the organic solvent into the aqueous solution. This is neither disclosed nor suggested in Violanto or Parikh. Consequently, it would not have been obvious to one of ordinary skill in the art to use sonication at a temperature below room temperature as an organic solvent removal method. Therefore, reconsideration and withdrawal of the § 103(a) rejection over Violanto in combination with Parikh of claims 1 and 25. Because claims 2-7, 11, 21-24, and 30-34 are dependant upon claim 1 and claims 26-29 and 35-38 are dependant upon claim 25 reconsideration of the § 103(a) rejection of claims 2-19, 21-38 is also respectfully believed to be appropriate.

Concerning the fourth § 103(a) rejection the Office suggests that Violanto in combination with Parikh in view of Popescu render applicants' claims 1-19 and 21-38 unpatentable. Here the Office further cites Popescu for the "teaching that it is well known in the art to use sonication as a method of solvent removal." However as, the applicants explained above in response to the second § 103(a) rejection, in the cited example Popescu uses heat and not sonication to evaporate solvent from their mixture. Therefore Popescu does not indicate that sonication as a method of solvent removal was a method known in the art. Also, none of these references teach sonication at below room temperature. Consequently, Violanto in combination Parikh would not have made the applicants' invention obvious to one of ordinary skill in the art. Therefore, reconsideration and withdrawal of the § 103(a) rejection over Violanto in combination with Parikh in view of Popescu of claims 1 and 25 are respectfully believed to be appropriate for these reasons. Because claims 2-7, 11, 21-24, and 30-34 are dependant upon claim 1 and claims 26-38 are dependant upon claim 25 reconsideration of the § 103(a) rejection of claims 2-19, 21-38 are also respectfully believed to be appropriate.

The applicants have earnestly endeavored to place application in condition suitable for allowance, and favorable consideration is respectfully requested.

Respectfully submitted,

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